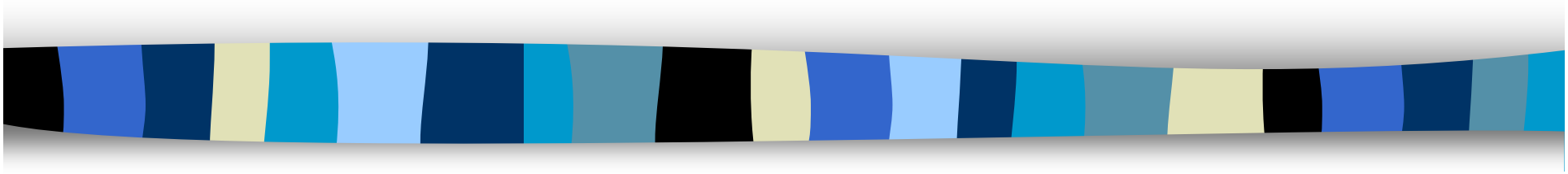
Informed Choice for Tissue Research



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Ethical and Legal Issues in Providing Biospecimens to a Biorepository

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Human Tissue Research

- What needs to be done to protect the safety and privacy of research subjects (including third parties) in tissue protocols?
- How does/should informed consent (choice) operate in this area?
- Short discussion with time for questions at the end.

Is Existing Tissue Research Exempt?

- 45 CFR 46.101(b): "…Research activities in which the only involvement of human subjects will be in one of the following categories are exempt: ...(4) Research involving the collection or study of existing …pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects." Some researchers mistakenly believe that any studies on existing pathology specimens are exempt. Exemption #4 does not apply to specimens that are linked to patient identity, even if the subject identifiers are locked up or kept by someone other than the researcher. It does not matter if the tissue would otherwise have been discarded. Many institutions require an IRB to determine whether or not the research is exempt.

Rules Governing Human Tissue

- Forensic
  - Federal or State Laws: Ex: Newborn screening. No consent. Why?
- Research
  - The “Common Rule” for Human Subject Protection 45 CFR 46
  - The role of IRB’s
    - Informed consent issues (which I will cover)

Collection of Tissue (1)

- Why was the tissue obtained?

1. Clinical purposes
2. Research purposes
3. Mixed

Collection of Tissue (2)

- Tissue is discarded, if:
  - Obtained for clinical purposes with proper consent
  - Released from a Tissue Procurement Core. Note: Malpractice issues if clinical tissue is not first analyzed by Pathology.

Collection of Tissue (3)

- Case Study:
  - Clinical tissue read as benign
  - Tissue requested for research
  - Tissue used in research
  - Tissue identified as NOT benign
- What if anonymous?
- What if identifiable?

The Elements of Consent

- 45 CFR 46.116 has the general rules while 46.117 has the documentation rules.
- The elements of consent are:

  1. A competent non-coerced subject with sufficient opportunity to understand the proposed research and decide whether or not to participate.

The Elements of Consent-2

2. No exculpatory language i.e. “You waive any rights you have to commercial profit from this research” vs. “No payment is available for this research or any commercial developments.”
3. The research, its potential benefits, foreseeable risks and alternatives

The Elements of Consent-3

4. Will confidentiality be maintained? How?
5. Is there any compensation?
6. Who can be contacted for answers?
7. Participation is voluntary and can be discontinued at any time. Q: What if tissue identifiers have been removed?

The Elements of Consent-4

8. Will “significant new findings” be provided to the patient?
9. What are the consequences if subject decides to withdraw?
10. The decision to participate or not will not result in any penalty or loss of subject’s otherwise entitled to benefits.

How to Discuss Risks?

- Obtaining the tissue is usually only minimal physical risk.
- The issue is how to discuss social risks: potential for loss of insurance, loss of job, loss of confidentiality even though there may be legal remedies for improper disclosure or improper use.

How to Discuss Risks?-2

- Ex: “Although we take pains to protect your privacy a tissue analysis may find its way into your medical record which may latter be disclosed by you to a life insurance company which may then deny or increase the cost of insurance based on research test results.”

Collection of Tissue: Tiered Consent

- Informed Consent Alternatives:
  1. No research use permitted
  2. Only anonymous research use
  3. Project specific use, no further contact
  4. Project specific use, contact for future use
  5. Project specific and related project use
  6. Project specific and other study use (allowable?)
  7. Commercial use

Banked Tissue Information

Date of Collection:	5/2/02
Pt. Name &/or Spec. #	3228
Sample Type:	Lung Biopsy Spec.
Consent obtained?	Yes
–Only for this study	No
–For related studies	Yes
–For any study	No
Recontact allowed	Yes

Commercial Sponsor Push-Back

- What if the commercial sponsor for your research says that they want to collect as many samples as possible with no tiered consent and at the end of your study you will be required to send all samples to the sponsor. The sponsor will add the samples to its data base.

Consent-Why Do We Need it?

- If the process of informed choice is carefully observed two things should happen:

1. You have, and can document, that the rules were followed.
2. You have created a supportive relationship between you and the subject with mutual trust and respect.

How to Classify and Store Tissue

- Tissue classifications:
  - Identified (linked)
  - De-identified research (coded)??
  - Anonymous research (unlinked)
- Issues, if identifiable:
  - Protect privacy
  - What information will be shared?
    - Anticipate important study findings (subject and family)
    - Anticipate unexpected findings (non-paternity, etc)

What is Anonymous?

- Subject's name, SS#, CPI number, any other identifier not on the record or sample label (including unique findings).
- Following collection there is no document anywhere, that is accessible by the researcher, which would link an assigned code to the subject's identity.
- After April 15, 2003 use the HIPAA elements for de-identification.

HIPAA De-identification

- Name
- Address (State is OK)
- Biometric ID/photo
- Dates (year is OK)
- Phone number
- Fax number
- E-Mail address
- Social Security #
- Med record #
- Health plan #
- Account #
- Certificate #
- Device #
- URL/IP #

Potential Problem Areas

- Anonymous versus linked samples
- Will research info find its way into the medical record?
- Sharing with other researchers
- Future use for other studies
  - Secondary use, or unclear use
- DNA banking (implied promises)
- Family consent (for medical history)??
- Withdrawal from study
- Study termination

Tissue Collection from Minors

- Is assent required?
- What happens when subject turns 18?
  - Recontact and consent required.
  - What if whereabouts unknown?
  - What do you do now?
    - Throw away specimen
    - Anonymize specimen
    - Hire a private detective

Consent Example #1

- I want your DNA to study Alzheimer's Disease. Your sample will not be identifiable. You will not get any results back. Anything I learn I will publish. Perhaps this will generate new knowledge from which you will benefit in the future. Do you want to participate?

Consent Example #2

- I want your DNA for the above described research, but I will keep your sample and in 5 years I may do some other not yet determined research. I will not re-contact you. Do you consent to participate?

- Should the IRB impose limits on the autonomy to consent?

To Share or Not to Share?

- Research findings
- Predictive genetic information
  - For person or family
- Confirmatory information
  - Contradictory information?
- Unanticipated findings
  - Misdiagnoses/missed dx.
  - Non-paternity
  - Other risks/diseases
- Evolving information
  - Where do responsibilities end?

Risk to the Subject from Disclosure of Genetic Information

- Impact on insurability
- Impact on employability
- Impact on sense of self
  - Social esteem
  - Deviation from “normal”
- Impact on future health risk
  - Can research findings be trusted?
  - Should research information guide clinical decision-making?

Risk to the Family from Disclosure of Genetic Information

- Previously undisclosed paternity or parentage
- Social esteem
- Anxiety about familial deviation from “normal”
- Survivor guilt
- Family secrets…..

Is there a Duty to Disclose Clinically Relevant Information?

- Case: Dr. IM Dubious does a research study on a cohort of 500 subjects looking for the gene that is responsible for colon cancer.
- The research finds a combination of genes that increase the risk of having colon cancer.
- Issue: Duty to disclose? To whom?

Duty to Disclose-2

- What if the samples were anonymous? Must the researcher tell the cohort there is a commercial test available?
- What if the samples are identifiable. Must the researcher tell the cohort their genetic analysis? What did the consent say? Does that matter now that the findings exist?

Duty to Disclose-3

- Malpractice analysis: Researcher has information that could benefit subject therefore there is a “duty to disclose” since failure could result in injury. Issues: Relationship is not physician-patient. What is the standard of care?
- Likely answer: Researcher could have intervened so has duty to do so.

Duty to Disclose-4

- Pate v. Threlkel (Fla. 1995). Daughter dx. with medullary thyroid carcinoma in 1990. Mother dx. in 1987. Suit against mother's doctor for failure to notify daughter. Held: There is a duty to warn which can be satisfied by talking to the patient who can then notify family members.

Duty to Disclose-5

- Compare: Safer v. Pack ((NJ 1996). In the 1950's father treated for colon cancer. In early 1990's daughter dx. with colon cancer. Claim: Hereditary disease so father's doctor should have warned family members. Held: Duty to warn patient and family exists. Issue: duty to warn v. privacy for patient??

Duty to Disclose-6

- Real issue: With the benefit of hindsight what ought to be done to lower known risks of heritable diseases.
- Is this like the duty to warn to prevent foreseeable injury (Tarasoff or patient with HIV having unprotected sex)? Does the duty trump confidentiality concerns? Both cases are pre-HIPAA privacy.

Does Consent Matter?

- What if subjects say that they don't care about "left-over" tissue and want it to be used for "good research"?
- Is consent for tissue different from consent for invasive research? Why? What is different about the risks?
- Do subjects really understand?

Waiver of Consent

- Under the “Common Rule” and the HIPAA Privacy regulations consent can be “waived” for a minimal risk study where it would be impracticable to obtain consent. Ex: Pathology has tissue blocks from the 1918 flu epidemic and a researcher wants to do a DNA analysis of the tissue.

Finding Tissue for Research

- The National Cancer Institute maintains a tissue bank with a searchable database that helps researchers locate specimens for research:

http://www.cancerdiagnosis.nci.nih.gov/specimens/finding.html#expediter.

The National Disease Research Interchange: http://www.ndriresource.org/.

Further Information

Office for Human Research Protections

- http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm for Repository guidance.

National Bioethics Advisory Commission (NBAC)

- Research Involving Human Biological Materials: Ethical Issues and Policy Guidance
- http://www.georgetown.edu/research/nrcbl/nbachome.html